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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,831	11/30/2006	Maria Kavallaris	69544-2	2175

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,831	KAVALLARIS, MARIA	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9, 16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/22/08, is acknowledged.

2. Claims 9 and 16-17 are pending and under examination in the instant application as they read on a method for inducing in a cell a resistance to an anti-microtubule agent comprising the step of providing in a cell, a mutant g actin.

3. The following new ground of rejection is necessitated by the IDS/amendment submitted 12/22/08.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "wherein the mutant g actin has an amino acid substitution located in sub-domain I of a wild-type γ actin" claimed in claim 9, lines 3-4 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 12/22/08 points to the specification at pages 39, lines 6-7 for support for the newly added limitations as claimed in claim 9. However, the specification does not provide a clear support for such limitation. It is noted that page 39, lines 6-7, discloses a specific mutation (V103 →L103) lies within sub-domain I. However, the claim is broaden to include any mutation in the sub-domain I of γ actin. Applicant is creating a new subgenus of γ actin mutations. A subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads, see *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

6. In view of the amendment filed on 12/22/08, only the following rejections are remained.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9 and 16-17 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for inducing in a cell a resistance to the antimicrotubule agent desoxyepothilone B or vinblastine, comprising the step of providing in a cell a mutant γ actin has the amino acid sequence of SEQ ID NO: 6 or 7; does not reasonably provide enablement for a method for inducing in a cell a resistance to "any anti-microtubule agent capable of disrupting microtubule dynamics" comprising the step of providing in a cell any "mutant γ actin, wherein the mutant g actin has an amino acid substituteion located in sub-domain I of a wild-type γ actin" in claim 9, wherein the mutant g actin has a sequence shown in SEQ ID NO: 6 wherein residue number 103 is leucine in claim 16 or SEQ ID NO: 7, wherein residue number 98 is leucine in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and usethe invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 7/2/08.

Applicant's arguments, filed 12/22/08, have been fully considered, but have not been found convincing.

Applicant submits that it is believed that sub-domain I is the site of various actin-binding proteins (see page 3, lines 26-38; and page 39, lines 6-7) and thus, the mutation would disrupt the binding abilities and confer the resistance. Applicants submit that claims 16 and 17 provide that either residue 98 or 103 are leucine. As one of ordinary skill in the art will appreciate, both of these amino acid substitutes occur in sub- domain I, which is taught by the specification to be the site of various actin binding proteins (See specification at page 3, lines 26-38 and page 39, lines 6-7). Therefore, with the teaching that an amino acid substitution in sub-domain 1 can confer resistance, one of skill in the art can appreciate that the claimed method is enabled for inducing cell resistance with the aforementioned mutant γ actin.

However, given that the sub-domain I is the site of <u>various</u> actin binding proteins. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2). Mutations in the conserved patterns without much change in the overall sequence would lead to a change in the essential active site structure and therefore to a change in function. Therefore, absent the ability to predict which of these substitution would function as claimed, and given the sub-domain I region critical for activity for various actin binding proteins, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

The skilled in the art would want to know which mutation would affect which binding protein. Accordingly, it is unpredictable which mutation in the actin sub-domain I would confer the induction of cell resistance to anti-microtubule agent. Moreover, Fojo (of record) teaches that mutations in structural γ actin protein have been identified in families with autosomal dominant hearing loss (see page 1345, 2nd col., top ¶ and page 1346, 2nd col., 1st full ¶). In fact, point mutations located in the sub-domain I of γ-acting case hearing loss.

Applicant submits that anti-microtuble agents bind to β-tubulin, typically disrupting microtubule dynamics leading to mitotic arrest and/or cell death (see page 5, lines 28-32). Thus, one of ordinary skill in the art can reasonably predict that an agent that disrupts the microtubule cytoskeleton within the cell could also have an affect, whether directly or indirectly, on the actin cytoskeleton. Conversely, one of ordinary skill in the art can reasonably predict that an agent that disrupts the actin cytoskeleton within the cell could also have an affect, whether directly or indirectly, on the microtubule cytoskeleton. Thus, the Examiner's reference to Fojo's comments on disruption of the microtubutes in vitro does not apply to the present application. Consequently, the Examiner's contention that the specification is not enabled for a method for inducing cell resistance to any anti-microtubule agent is incorrect.

However, the Examiner notes that there is no requirement in the claims that the anti-microtuble agents binds β-tubulin. The claim recites that the agents capable of disrupting microtubule dynamics. The agents can bind to microtubule, α-tubulin or microtubule associated protein and still capable of disrupting microtubule dynamics. Claim terms are interpreted not only in light of the specification but also in light of the prior art. See In re Cortright, 49 USPQ2d 1464, 1467 (Fed. Cir. 1999). Regarding Fojo's comments on disruption of the microtubules in vitro, Applicant dismisses the teaching as does not apply to the present application. However, Applicant does not dispute the Fojo's teachings with respect to the anti-microtubules agents that do not require actin for their function to disrupt microtubule dynamics.

Applicant submits that the post-dated references cited by the Examiner provide methods to confer cell resistance to microtuble agents on *in vivo* derived samples were accomplished through routine experimentation.

The Examiner agrees with applicant that the references use the *in vivo* derived samples, i.e., *in vitro*.

Applicant argues in conjunction with case law that it is recognized in the art that development of any new treatment entails in vitro experiments prior to in vivo studies. If the in vitro results were as unreliable in terms of predicting in vivo results as the Examiner suggests, then nothing would proceed from the in vitro stage to testing in humans. There can be no question that Applicants' use of an in vitro model is entirely appropriate, as such models are both accepted and commonly used in the art to study human neoplastic disease as the in vitro model is clinically predictive of the ability to accomplish the method in vivo with a similar methodology.

However, there must be a rigorous correlation of pharmacological activity between the disclosed in vitro utility and an in vivo utility to establish practical utility. In order to practice Applicant's claimed method in vivo, a cell based therapy is must be used. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. In addition, applicant's experimental results have relied on specific tumor cell lines. It is not clear that such cell lines adapted for culture in vitro would reflect the therapeutic barriers presented by neoplastic cells in a clinical setting.

Moreover, it is unclear why one would perform such method *in vivo*. Since inducing resistance to an anti-microtubule agent such as vinblastine or desoxyepothilone B would lead to clinical failure. That is induction of resistance to an anti-microtubule would lead reduced efficacy of anti-microtubule therapy. It is unclear what conditions are targeted for such therapy.

Again, it is the Examiner's the specification lacks a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims. If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied.

"There is no evidence of record that experimental animal models have been developed in this area which would be predictive of human efficacy." Ex parte Balzarini, 21 USPQ2d 1892.

9. Claims 9 and 16-17 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 7/2/08.

Applicant is in possession of for an *in vitro* method for inducing in a cell a resistance to the antimicrotubule agent desoxyepothilone B or vinblastine, comprising the step of providing in a cell a mutant γ actin has the amino acid sequence of SEQ ID NO: 6 or 7.

Applicant is not in possession of for a method for inducing in a cell a resistance to any "antimicrotubule agent capable of disrupting microtubule dynamics" comprising the step of providing in a cell any "mutant γ actin, wherein the mutant γ actin has an amino acid substituteion located in sub-domain I of a wild-type γ actin" in claim 9, wherein the mutant g actin has a sequence shown in SEQ ID NO: 6 wherein residue number 103 is leucine in claim 16 or SEQ ID NO: 7, wherein residue number 98 is leucine in claim 17.

Applicant's arguments, filed 12/22/08, have been fully considered, but have not been found convincing.

Applicant asserts that the claims, as amended, recite that mutant y actin has an amino acid substitution located in sub-domain I of a wild-type γ actin, which is believed to be the site of various actin-binding proteins. One of skill in the art can envision the contemplated γ actin mutant possibilities because there is a correlation between the structure and activity of inducing resistance to an anti-microtubule agent. The structure of having a mutation within the site of actin-binding proteins to disrupt binding is correlated to the activity of inducing resistance. In light of the foregoing, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Again, sub-domain I of γ actin is the site of various actin-binding proteins. Since there is no information regarding which amino acid residues within the sub-domain I of γ actin are responsible for inducing resistance to an anti-microtubule agent, very little is known about the γ actin, and only SEQ ID NO: 6 and 7 species is disclosed. Given that the core structure "sub-domain I" of γ actin is the site of various actin-binding proteins, substitution within subdomain I of γ actin would effect site of other actin-binding proteins.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 5, 2009

/Maher M. Haddad/
Maher M. Haddad, Ph.D.
Primary Examiner

Technology Center 1600